

### REMARKS

Claim 20 is pending in the application. Claims 1-19 and 21-33 have been cancelled. New claims 34-37 are hereby added.

Claim 20 has been rejected as being indefinite under 35 U.S.C. § 112, ¶ 2, and has been rejected for lack of enablement under 35 U.S.C. § 112, ¶ 1.

Claim 20 has also been rejected as being: (1) anticipated or rendered obvious by *Qu, et al., Proc. Natl. Acad. Sci. USA, Vol. 92, pp. 10277-10281 (October 1995) ("Qu")*; (2) anticipated by *Lee, et al., Structure, 1995 3(12), 1333-40 ("Lee")*; and (3) anticipated by United States Patent Application Document No. 2003/0054440 ("*Mayo*").

Applicants traverse each of the outstanding grounds of rejection and maintain for the reasons which follow that claim 20 and new claims 34-37 are definite, enabled, patentable over the prior art, and in a condition for allowance.

#### **1. New Claims 34-37.**

New claims 34-37 do not contain new matter. Support for new claims 34-37 is found in the specification of the instant application as originally filed, e.g., in Example 1 at pages 18-25. New claims 34-37 do not raise issues requiring further consideration or search by the Examiner beyond that required in connection with claim 20.

New claims 34-37 particularly point out and distinctly claim methods of the invention which evaluate the binding of a composition to an  $\alpha 1\beta 1$  integrin  $\alpha 1$ -I domain using the crystal coordinates of a crystallized  $\alpha 1$ -I domain. In the methods of new claims 34-37, the  $\alpha 1$ -I domain is digested proteolytically prior to crystallization and competition assays are used to assess the extent to which a composition binds to the  $\alpha 1$ -I domain.

#### **2. Claim 20 and New Claims 34-37 Are Definite and Enabled.**

##### **(a) Claim 20 and New Claims 34-37 Are Definite.**

Claim 20 as amended overcomes each of the indefiniteness objections raised by the Examiner in the December 8, 2004 Office Action. New claims 34-37 are also definite and satisfy the statutory criteria of 35 U.S.C. § 112, ¶ 2.

Amended claim 20 particularly points out and distinctly claims a method in which: (1) crystallographic coordinates of the  $\alpha 1\beta 1$  integrin  $\alpha 1$ -I-domain are used in a fitting operation to assess whether a composition will associate with the  $\alpha 1$ -I-domain; and

(2) the degree of such association is determined using a competition assay. Support for the instant amendments to claim 20 is found in the specification of the instant application as originally filed, e.g., in Example 1 at pages 18-25.

**(b) Claim 20 and New Claims 34-37 Are Enabled.**

The Examiner rejected claim 20 for lack of enablement on grounds that while the specification is enabling for the use of rat  $\alpha$ 1-I-domain crystallographic coordinates, it does enable the use of  $\alpha$ 1-I-domain crystallographic coordinates from non-rat sources. *Drenth* is cited by the Examiner to show how uncertain crystallization of  $\alpha$ 1-I-domain proteins allegedly was as of the effective filing date of the instant application. Per the Examiner, it would have required undue experimentation as of the effective filing date for those of ordinary skill in the art to determine the crystallographic coordinates of non-rat  $\alpha$ 1-I-domains.

Read fairly, *Drenth* undercuts the Examiner's assertion that claim 20 is nonenabled. *Drenth* discloses that "crystal growth is mainly a trial and error process". *Drenth* at p. 19. (See also *Drenth* at p. 1: "Protein crystallization is mainly a trial-and-error procedure....") Rather than suggest that claim 20 is nonenabled, *Drenth* discloses that skilled artisans should focus on protein purity to improve their chances of obtaining a desired crystal and can increase their odds of success by optimizing conditions determined through multiple experiments. *Id.* at pp. 1, 2-3. Further, *Drenth* describes alternative crystallographic techniques involving factorial design and highlights sources of relevant information on the crystallization of biological macromolecules. *Id.* at p.7.

The fact that significant experimentation may be required along the lines of *Drenth's* trial and error approach does not support a finding that claim 20 is only enabled for the exemplified rat  $\alpha$ 1-I-domain. A claimed invention may be enabled even though substantial experimentation is required, particularly where - as here - the specification provides ample guidance to skilled artisans on how to select and employ useful crystallization conditions and reactants. See, e.g., Specification, page 21, lines 10-22. See also *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558 (Fed. Cir.1996); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367

(Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987)(extensive experimentation does not, *per se*, equate to nonenablement).

*Qu* and *Lee* also refute the Examiner's position on enablement. While both references are patentably distinguishable from the claimed methods, as explained hereinafter, they show that skilled artisans were able to crystallize  $\alpha 1$ -I-domains of other mammalian integrins.

Accordingly, the specification of the instant application enables those of ordinary skill in the art to make and use the claimed invention. It would not have required undue experimentation by skilled artisans to determine non-rat  $\alpha 1$ -I-domain crystallographic coordinates in order to practice the methods of claim 20 and new claims 34-37.

**3. Claim 20 and New Claims 34-37 Are Patentable Over *Qu*.**

**(a) *Qu* Is Not Anticipatory.**

*Qu* does not relate to screening methods such as those of the pending claims. Rather, *Qu* determined the high affinity configuration of the I-domain of a completely different integrin.

*Qu* determined the high-resolution crystalline structure of the I-domain of CD11a. CD11a is an integrin alpha-L precursor. CD11a is not an  $\alpha 1\beta 1$  integrin and the Examiner is incorrect when he maintains that *Qu* described crystallographic coordinates of an  $\alpha 1\beta 1$  integrin  $\alpha 1$ -I-domain.

Use of crystallographic coordinates of an  $\alpha 1\beta 1$  integrin  $\alpha 1$ -I-domain constitutes a limitation of claim 20 and new claims 34-37. *Qu* does not disclose that limitation, either expressly or inherently.

Not only does *Qu* fail to disclose the use of crystallographic coordinates of an  $\alpha 1\beta 1$  integrin I-domain, the reference also does not describe a fitting operation between an  $\alpha 1\beta 1$  integrin I-domain and a composition. *Qu* disclosed that the manganese-bound form of CD11a represents a high-affinity state of the molecule. Determining that a cationic form of an I domain has the highest binding affinity is not the same as determining whether a certain molecule - based on crystallographic coordinates of a particular I domain - is likely to bind to that I domain

Further, *Qu* does not disclose using a competition assay to assess the extent to which a composition binds to the  $\alpha 1$ -I domain, as required in the methods of the pending claims.

Because *Qu* does not disclose each and every limitation of claims 20 and 34-37, it does not anticipate those claims as a matter of law. *Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339 (Fed. Cir. 2000)(to anticipate, a prior art reference must disclose each and every limitation of the claimed invention).

**(b) The Claimed Methods Are Not Obvious In Light of Qu.**

The Examiner asserts that it would have been *prima facie* obvious to use *Qu*'s I-domain crystallographic coordinates to identify the interaction of an  $\alpha 1\beta 1$  integrin with its ligands. The fundamental flaws in this position have already been pointed out: *Qu* dealt with a different integrin and has nothing to do with screening compositions for use as potential inhibitors or activators of an integrin I domain.

*Qu* did not disclose  $\alpha 1\beta 1$  integrin  $\alpha 1$ -I domain crystallographic coordinates; did not describe how to use those coordinates to identify compositions which would bind to an  $\alpha 1\beta 1$  integrin  $\alpha 1$ -I domain; and did not describe how to assess the degree of binding of a composition to an  $\alpha 1\beta 1$  integrin  $\alpha 1$ -I domain. Therefore, *Qu* does not establish a *prima facie* case of obviousness as it lacks the aforementioned key limitations of claims 20 and 34-37 and there is no basis in the prior art which would have motivated skilled artisans to fundamentally alter *Qu* to include those limitations. *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993)(a *prima facie* case of obviousness is only established where the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art).

There is no support for the notion that *Qu* would have lead those of ordinary skill in the art to identify the crystallographic coordinates of a different ligand, use those coordinates to identify compositions which might bind to the different ligand, and use a competition assay to assess the extent to which the composition binds to the different ligand. Such a fundamental revision of *Qu* would require the impermissible hindsight use of the claimed methods. *In re Kotzab*, 217 F.3d 1365 (Fed. Cir. 2000). Again, the

limitations of claims 20 and 34-37 cannot be read into *Qu* as the prior art does not disclose or suggest them. *Rijckaert, supra*.

**4. Claim 20 and New Claims 34-37 Are Patentable Over *Lee* and *Mayo*.**

Like *Qu*, *Lee* does not relate to screening methods such as those of the pending claims. Rather, like *Qu*, *Lee* determined the high affinity configuration of the I-domain of a completely different ligand.

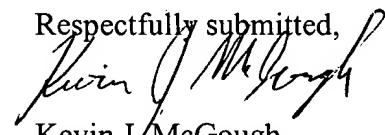
*Lee* determined the crystallographic coordinates of the I-domain of CD11b and also concluded that manganese-bound forms of that I-domain represent the high-affinity state of the protein. CD11b is not an  $\alpha 1\beta 1$  integrin. Therefore, *Lee* does not anticipate claim 20 or new claims 34-37 for the same reasons that *Qu* does not anticipate those claims. *Lee* fails to disclose the use of crystallographic coordinates of an  $\alpha 1\beta 1$  integrin I-domain, does not describe a fitting operation between an  $\alpha 1\beta 1$  integrin I-domain and a composition, and does not disclose using a competition assay to assess the extent to which a composition binds to the  $\alpha 1$ -I domain.

*Mayo* is not prior art to the claims of the instant application. *Mayo's* effective filing date is July 7, 2000 and *Mayo* did not publish until March 20, 2003. The effective filing date of the claims of the instant application is October 6, 1998. The anticipation rejection based on *Mayo* is therefore improper and should be withdrawn.

**5. Summary.**

In light of all of the foregoing, Applicants submit that claim 20 as amended and new claims 34-37 are patentable and are in a condition for allowance. Applicants respectfully request that claim 20 and new claims 34-37 be passed to issue.

Respectfully submitted,



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